REMARKS

Entry of the foregoing, reexamination and further and favorable reconsideration of the subject application in light of the following remarks, pursuant to and consistent with 37 C.F.R. § 1.112, are respectfully requested. Applicants wish to thank the Examiner for graciously granting an interview on May 9, 2001 and for her time and useful comments.

The Office Action Summary correctly indicates that claims 1-28 are pending in the application. Claims 1-28 are subject to a restriction requirement. Claims 14-28 are withdrawn from consideration. Claims 1-13 are under consideration and stand rejected.

Claims 1, 5 and 9-13 have been amended.

Claim 1 has been amended to more clearly describe the claimed subject matter. Support for the amendments to claim 1 can be found in the specification in at least page 21, lines 5-17, and at page 10, lines 22-25.

Claim 5 has been amended to more clearly describe the claimed subject matter. Support for these amendments may be found in at least page 21, lines 5-17, page 14, lines 3-14, and page 34, lines 15-24.

Claims 9 and 10 have been amended to more clearly describe the claimed subject matter. Support for these amendments can be found in at least page 13, lines 3-10, page 21, lines 5-17, page 23, lines 7-18, and page 34, lines 15-24.

Claims 11-13 have been amended to more clearly describe the claimed subject matter. Support for these amendments may be found at least in pages 72-74.

Claims 29-50 have been added by the present amendment. Support for these claims is derived from throughout the specification and the claims as originally filed with particular reference to at least the above described portions as well as page 10, lines 5-9, and page 38, lines 3-16.

No prohibited new matter has been introduced by way of the above amendments. Applicants reserve the right to file a continuation or divisional application on subject matter canceled by way of this Amendment.

I. Rejections withdrawn

Examiner has withdrawn the previous rejection of claims 1-13 under 35 U.S.C. § 112, second paragraph and the rejection of claims 1,5,9 and 10 under 35 U.S.C. § 101 and 35 U.S.C. § 112, first paragraph. Examiner concedes that the claimed nucleic acid sequence has utility for detection of the pathogen.

II. Rejections under 35 U.S.C. § 101 and 35 U.S.C. § 112, first paragraph

Claims 2-4, 6-8, and 11-13 remain rejected under 35 U.S.C. § 101 and 35 U.S.C. § 112, first paragraph, for reasons presented in paragraphs 10 and 11 of the Office Action mailed July 13, 2000 (paper 14).

In paper 14, it was asserted that the claimed invention was not supported by a specific, credible, and substantial utility or a well established utility. It was further asserted that no specific functions are defined for the protein or polypeptide. The Examiner referred to page 53, line 7 and Table 2 to assert that the only "putative" identification is as a "hypothetical protein". It was asserted that the polypeptide encoded by SEQ ID NO: 1394 (amino acid sequence SEQ ID NO: 7056) is "not characterized as having enzymatic, adhesive characteristic, toxin activity or correspondence to any other to any other proteins which are known to be associated with similar types of bacteria."

Applicants respectfully disagree with the assertion that no specific, credible, and substantial utility is asserted for the polypeptide product of SEQ ID NO: 1394. While the specification does disclose a multitude of useful polypeptides, one of skill in the art is taught the specific utility of the polypeptide product of the presently claimed invention by the disclosed sequence, the annotation in Table 2, and the specification.

Below, Applicants present a detailed illumination of this assertion in the present application. In overview, a specific and substantial utility is asserted by at least these elements of the specification.

1. Disclosing the primary structure of the polypeptide product of the claimed nucleic acid sequence.

2. Disclosing a homology based functional identification and teaching the manner in which this information may be relied upon to appreciate the polypeptide's function.
3. Teaching that well understood and routine reference to public databases may be relied upon for appreciation of the function of the subject of the presently claimed invention from the disclosed primary structure and functional identification.
4. Disclosing that the polypeptide product of the presently claimed invention is a pseudouridine synthase, which was understood in the art to be essential to cellular function.
5. Teaching that enzymes which perform essential functions have utility at least as research tools for development of compounds which inhibit the growth of a pathogen.
6. The credibility of this assertion is finally shown to be demonstrated by a publication (Koonin, E.V. (1996), Nucleic Acids Research (Oxford University Press), 24:2411-15, attached) describing pseudouridine synthases. This publication is also evidence that one of skill in the art could have immediately appreciated that the presently claimed invention had a well established utility solely from its disclosed primary structure.

The primary structure of the polypeptide product of the presently claimed invention and its biological function is disclosed as follows. The primary structure of the polypeptide encoded by SEQ ID NO: 1394 is SEQ ID NO: 7096 as disclosed in the Sequence Listing. The open reading frame disclosed in SEQ ID NO: 1394 comprises a sequence of the *E. cloacae* genome from a first stop codon to a second stop codon. At page 38, lines 6-11 one of skill in the art is reminded that translation initiation sites correspond to ATG, GTG, and TTG. There are three such initiation sites within the first 13 codons of SEQ ID NO: 1394 which ends with a stop codon. Whereas this is a bacterial coding sequence, no introns may interrupt the sequence. Thus, one is taught the primary structure of the polypeptide encoded by SEQ ID NO: 1394.

The function of the polypeptide encoded by SEQ ID NO: 1394 is disclosed by reference to Table 2. At page 37, line 16 through page 39, line 13 the specification

presents a description of the contents of Table 2 as follows. The first four columns (1-4) of Table 2 identify the sequence by the number of the contig from which the sequence is derived, a designation for the ORF, and SEQ ID numbers for the nucleotide and corresponding amino acid sequence respectively. The next two columns (5, 6) of Table 2 describe the nucleotide and amino acid lengths respectively. The remaining columns contain homology scores and homolog identifying information which the specification discloses for the expressed purpose of describing the biological function of the polypeptide products of the nucleic acid sequences. Column seven provides the BLAST score for the cited homology match wherein higher numbers reflect a better match. A more quantitative "P-value" is given in column eight. The P-value is the probability that the match is not significant. A P-value near zero reflects a high likelihood that the match is meaningful. Column nine provides an accession number or an internal identifier if no accession number is available. And finally, column ten provides descriptive text for the match.

In Table 2, the BLAST identified homology between SEQ ID NO: 1394 (and its associated polypeptide) with the *ymfc* gene (b1135) of *E. coli* is identified. Applicants note that it is the product of the *E. coli* ymfc gene which was identified as a "hypothetical" protein in Table 2 and not the product of SEQ ID NO: 1394 as asserted in the Office Action mailed July 13, 2000 (paper 14). By reference to public databases known to and routinely used by one of skill in the art, one would have appreciated that this information identifies the polypeptide product as a pseudouridine synthase of the RsuA family. For example, SWISSPROT entry Accession No. P75966 (NCBI entry PID gi:2501525 and gi:3916025) created November 1, 1997 contains the comments "[SIMILARITY] STRONG, TO H.INFLUENZAE HI0694. [SIMILARITY] BELONGS TO THE RSUA FAMILY OF PSEUDOURIDINE SYNTHASE." A copy of NCBI entry gi:2501525 is appended hereto as Exhibit A.

Referring to page 53, at about line 7 of the specification, it was asserted in the Official Action of July 7, 2000 (Paper 14) that the homology identification in Table 2 is merely "putative". In the context of page 53, the specification is describing all the entries in Table 2. The degree to which this adjective applies to each identification in Table 2 and

to the claimed nucleic acid sequence in particular is shown quantitatively by the disclosed P-value. The P-value of $9x10^{-95}$ in column 8 of the Table 2 entry for SEQ ID NO: 1394 reflects a very high degree of confidence in the disclosed identification.

The function of a polypeptide sequence is routinely determined in the art by reference to homologous sequences and conserved motifs. For instance, at page 48, line 19 through page 49, line 9 the specification teaches the use of routine computer-assisted procedures by which one of skill in the art may ascertain the function of the claimed polypeptide with specific teaching of the importance of small conserved motifs for appreciating the function of a polypeptide. At page 53, lines 2-13 the specification teaches that one of skill in the art may use the polypeptide products of the present invention for commercial and industrial purposes consistent with such an identification.

Public database entries of conserved sequence motifs known to one skilled in the art (see for example PROSITE Accession No. PDOC00885 and PS01149, attached as Exhibit B) demonstrate that conserved motifs also identify the polypeptide product of the claimed invention as a member of the RsuA family of psuedouridine synthases.

Additionally, psuedouridine synthases were known to have certain conserved signature motifs (see for example: Koonin, E.V. (1996), Nucleic Acids Research (Oxford University Press), 24:2411-15, attached as Exhibit C.) These motifs are readily apparent upon inspection of the disclosed SEQ ID NO: 7056 as demonstrated in the following sequence.

Ala Ile Met Arg Gln Leu Ile Thr Pro Glu Asn Thr Met Thr Lys Thr
1 5 10 15
Ser Phe Arg Lys His Arg Val Glu Arg Phe Ser Ser Arg Gln Ala Thr
20 25 30
Arg Arg Thr Pro Glu Pro Gln Pro Thr Arg **Val** **Ile** **Leu** **Phe** **Asn** **Lys**
35 40 45
Pro Tyr Asp **Val** **Leu** Pro Gln Phe Thr Asp Glu Ala Gly Arg Ser Thr
50 55 60
Leu Lys Asp Phe Ile Pro Val Gln Gly Val Tyr Ala Ala *Gly* ***Arg*** ***Leu***
65 70 75 80
Asp Arg Asp ***Ser*** Glu ***Gly*** ***Leu*** ***Leu*** ***Val*** ***Leu*** *Thr* *Asn* Asp Gly Val Leu
85 90 95
Gln Ala Arg Leu Thr Gln Pro Gly Lys Arg Thr Gly Lys Ile Tyr Tyr
100 105 110
Val Gln Val Glu Gly Glu Pro Asp Asp Ala Ser Leu Ala Lys Leu Arg
115 120 125
Asn Gly Val Thr Leu Asn Asp Gly Pro Thr Leu Pro Ala Gly Ile Glu
130 135 140
Arg Val Asn Glu Pro Glu Trp Leu Trp Pro Arg Asn Pro Pro Ile Arg
145 150 155 160
Glu Arg Lys Ser Ile Pro Thr Ser Trp **Leu** Lys **Ile** Thr Leu Tyr Glu
165 170 175
Gly **Arg** Asn Arg **Gln** **Val** **Arg** Arg **Met** Thr Ala His **Val** **Gly** Phe Pro
180 185 190
Thr **Leu** Arg Leu Ile Arg Tyr Ala Met Gly Ser Tyr Thr Leu Asp Ser
195 200 205
Leu Ala Asn Gly Glu Trp Arg Asp Val Thr Pro Lys Glu Asn
210 215 220

In the above, three conserved motifs I (43-53), II (79-90), and III (170-194) are identified, the bold residues are conserved bulky hydrophobic residues (I, L, V, M, F, Y, W) and the bold **underlined** residues are consensus sequence residues as reported by Koonin. The PROSITE PSI_RSU Rsu family of pseudouridine synthetase signature consensus pattern (residues 78-92) is identified by *italics*. Thus, one of ordinary skill in the art could have appreciated that the presently claimed invention has a well established utility solely by the disclosure of SEQ ID NO: 1394 and SEQ ID NO: 7056 alone.

Koonin teaches that psuedouridine synthases perform essential functions in all cells. Enzymes which perform essential functions are useful targets for antibacterial drugs. Thus, the polypeptide product of the claimed invention is useful for screening candidate drugs as described at least on pages 80-81 of the specification.

In at least the above portions of the specification, a specific and substantial utility for the disclosed polypeptide product of the claimed invention is asserted by the Applicants. Accordingly, Applicants request that the rejection of at least claims 2-4 and 6-8 under 35 U.S.C. § 101 be withdrawn. And, whereas the Examiner has agreed that the disclosure is enabling for the vectors, cells, and methods of claims 2-4, and 6-8, Applicants respectfully request the withdrawal of the rejection of these claims under 35 U.S.C. § 112, first paragraph.

Claims 11-13 remain rejected under 35 U.S.C. § 112, first paragraph, because the it is asserted that use of the claimed compositions as a vaccine is unpredictable. Without conceding to the Examiner's assertion, claim 11 has been amended to recite "A composition comprising the nucleic acid of claim 5 and a pharmaceutically acceptable carrier." Dependent claims 12 and 13 have been amended to recite the above composition further comprising an adjuvant and/or one or more pharmaceutically active ingredients. As amended, claims 11-13 as amended are not subject to a scope of enablement rejection over the predictability of DNA vaccines. Accordingly, Applicants respectfully request the withdrawal of the rejections of claims 11-13 under 35 U.S.C. § 112, first paragraph.

New claims 29, 33, 34, 38, 42, and 46 are drawn to embodiments of the nucleic acid sequence of the present invention and therefore have utility and are enabled as already established. New claims 30-32, 35-37, 39-41, and 43-45 are drawn to expression vectors, host cells, and methods of expression and are believed to have an asserted utility and be enabled for at least the reasons set forth above.

III. Prior Rejections under 35 U.S.C. § 102(b)

Claims 1, 5 and 10 remain rejected under 35 U.S.C. § 102(b) as being anticipated separately by each of Haertl, R. *et al.* (1993) *J. Clin. Microbiology,* 31:128-33; Matsutani, S. *et al.* (1991), *J. Bact.*, 173:7802-09; or Lambert-Zechovsky et al. (1992), *Clin. Infect. Dis.*, 15:30-2 on the grounds that the claimed isolated nucleic acid comprising SEQ ID NO: 1394 reads on isolated *E. cloacae* chromosomal or total DNA disclosed in each reference. First, the references do not disclose SEQ ID NO: 1394. Second, claims 1, 5 and 10 have been amended to more clearly describe the claimed subject matter by better characterizing the **isolated** nucleic acid in harmony with the definition on page 21, lines 5-17 of the specification.

The definition of isolated nucleic acid which appears on page 21 at line 5 of the specification reads as follows:

> A purified or isolated or a substantially pure nucleic acid, e.g., a substantially pure DNA, (are terms used interchangeably herein) is a nucleic acid which is one or both of the following: not immediately contiguous with both of the coding sequences with which it is immediately contiguous (i.e., one at the 5' end and one at the 3' end) in the naturally-occurring genome of the organism from which the nucleic acid is derived; or which is substantially free of a nucleic acid with which it occurs in the organism from which the nucleic acid is derived.

Claims 1, 5 and 10 as amended incorporate language from the above definition to better characterize the claimed **isolated** nucleic acids. As amended, claims 1, 5 and 10 cannot read on chromosomal or total DNA as disclosed in the references. The references do not teach or suggest an isolated nucleic acid comprising SEQ ID NO: 1394 of the present invention as claimed. Therefore, the references do not anticipate the present invention. Accordingly, Applicants respectfully request the withdrawal of rejections of claims 1, 5 and 10 under 35 U.S.C. § 102(b) over Haertl, R. *et al.* (1993), Matsuni, S. *et al.* (1991), and Lambert-Zechovsky et al. (1992).

New claims 29, 33, 34, 38, 42 and 46 are drawn to embodiments of the nucleic acid sequence of the present invention. Claims 29, 33 and 46 incorporate the above characterizing language to clearly distinguish the presently claimed invention from total

chromosomal DNA. Claims 38 and 42 recite closed language and are clearly distinguishable over the prior art. New claims 30-32, 35-37, 39-41, and 43-45 are drawn to expression vectors, host cells, and methods of expression and are not anticipated by the prior art.

IV. Rejections under 35 U.S.C. § 112, second paragraph

Claims 1, 5, 9 and 10 stand rejected under 35 U.S.C. § 112, second paragraph as indefinite for the reciting both "comprising" and "is". Claims 1, 5, 9 and 10 have been amended to more clearly recite the intended open language and to better characterize the claimed nucleic acid or probe. Accordingly, Applicants respectfully request withdrawal of the rejection of claims 1, 5, 9 and 10 under 35 U.S.C. § 112, second paragraph.

V. New rejections under 35 U.S.C. § 102(b)

Claims 5 and 9 stand rejected under 35 U.S.C. § 102(b) as being anticipated by Blattner *et al.*, (EMBL entry Accession No. AE000213, January 29, 1997) or Oshima *et al.* (EMBL entry Accession No. ECD748, October 31, 1996). The Examiner asserts that Blattner *et al.* and Oshima *et al.* each disclose isolated DNA molecules encoding a polypeptide which share identity over 52 consecutive amino acid residues. The Examiner asserts that this corresponds to 156 nucleic acids in common with SEQ ID NO: 1394. Applicants respectfully point out that the referenced DNA sequences are not identical for more than 23 sequential nucleotide base pairs. Claims 5 and 9 have been amended to more clearly characterize the claimed subject matter. Claims 5 and 9 as amended are drawn to an isolated nucleic acid which comprises at least 25 sequential bases of SEQ ID NO: 1394. Whereas the reference sequences do not share more than 23 sequential identical nucleotides, the reference cannot anticipate claims 5 and 9. Applicants therefore respectfully request withdrawal of the rejection of claims 5 and 9 under 35 U.S.C. § 102(b).

New claims 29, 33, 34, 38, 42 and 46 are drawn to embodiments of the nucleic acid sequence of the present invention. Claim 29 is drawn to a nucleic acid which encodes a polypeptide of *E. Cloacae* found in SEQ ID NO: 7056. The translated polypeptide

sequence of the nucleic acids disclosed by Blattner *et al.* and Oshima *et al.* is a polypeptide of *E. coli* which is homologous to SEQ ID NO: 7056. The nucleotide encoding the polypeptide of the prior art does not encode a polypeptide of *E. cloacae* consisting of a range of residues which is 3 - 222, 6 - 222, or 13 - 222 of SEQ ID NO: 7056. Claim 29 is therefore not anticipated.

The amino acid sequence homology identified by the Examiner is 85.6% over 216 residues of SEQ ID NO: 7056. Claims 33 and 34 are drawn to an isolated nucleic acid encoding a polypeptide which comprises at least 90% and 95% sequence identity with SEQ ID NO: 7056 respectively. Claims 33 and 34 are therefore distinguished from the nucleic acid sequences disclosed by Blattner *et al.* or Oshima *et al.* Claims 38 and 42 are drawn to the nucleic acid of SEQ ID NO: 1394 or three well defined fragments thereof. Neither Blattner *et al.* or Oshima *et al.* disclose SEQ ID NO: 1394, and thus claims 38 and 42 are clearly distinguishable over the prior art. Claim 46 is drawn to a probe comprising at least 30 sequential nucleotides of SEQ ID NO: 1394 and is not anticipated by Blattner *et al.* or Oshima *et al.* for at least the reasons set forth above. New claims 30-32, 35-37, 39-41 and 43-45 are drawn to expression vectors, host cells, and methods of expression and are not anticipated by the prior art.

CONCLUSION

In view of the foregoing, further and favorable action in the form of a Notice of Allowance is believed to be next in order. Such action is earnestly solicited.

In the event that there are any questions relating to this application, it would be appreciated if the Examiner would telephone the undersigned attorney concerning such questions so that prosecution of this application may be expedited.

Respectfully submitted,

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Date: June 22, 2001

Attachment to Amendment dated June 22, 2001

Marked-up Claims 1, 5 and 9-13

1. (Twice Amended) An isolated nucleic acid [comprising a nucleotide sequence] encoding an *E. cloacae* polypeptide wherein the nucleic acid comprises [and is] SEQ ID NO: 1394, and wherein SEQ ID NO: 1394 is not immediately contiguous with both of the coding sequences with which it is immediately contiguous in the naturally-occurring *E. cloacae* genome.

5. (Twice Amended) An isolated nucleic acid [comprising a nucleotide sequence] encoding an *E. cloacae* polypeptide or a fragment thereof, wherein the nucleic acid comprises at least 25 sequential bases of [said nucleic acid is] SEQ ID NO: 1394, and wherein SEQ ID NO: 1394 is not immediately contiguous with both of the coding sequences with which it is immediately contiguous in the naturally-occurring *E. cloacae* genome.

9. (Twice Amended) A probe comprising a nucleotide sequence including at least 25 sequential nucleotides of [consisting of at least 8 nucleotides of] SEQ ID NO: 1394 , wherein SEQ ID NO: 1394 is not immediately contiguous with both of the coding sequences with which it is immediately contiguous in the naturally-occurring *E. cloacae* genome.

10. (Twice Amended) An isolated nucleic acid comprising a nucleotide sequence of at least 30 consecutive [8] nucleotides in length, wherein the sequence [is hybridized] can hybridize under conditions of high stringency to a nucleic acid comprising SEQ ID NO: 1394 which encodes a biologically active polypeptide of *E. cloacae*, and wherein the isolated nucleic acid sequence is not immediately contiguous with both of the coding sequences with which SEQ ID NO: 1394 is immediately contiguous in the naturally-occurring *E. cloacae* genome.

Attachment to Amendment dated June 22, 2001

Marked-up Claims 1, 5 and 9-13

11. (Amended) A [vaccine] composition [for prevention or treatment of an *E. cloacae* infection] comprising [an effective amount of a] the nucleic acid of claim 5 and a pharmaceutically acceptable carrier.

12. (Amended) A [vaccine] composition of claim 11, further comprising an adjuvant.

13. (Amended) A [vaccine] composition of claim 11, further comprising one or more pharmaceutically [additional] active ingredients.